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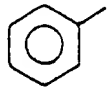
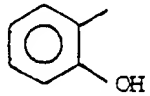
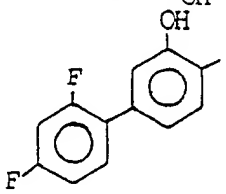
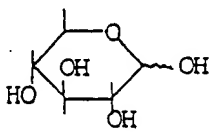
(54) Title: AMINO-SALICYLIC ACID DERIVATIVES AND PHARMACEUTICAL COMPOSITIONS

(57) Abstract

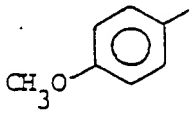
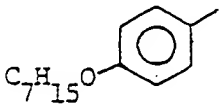
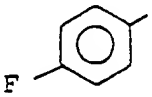
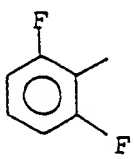
(5-Acylamino-2-hydroxy)benzoic acid and salts thereof with imidazole, substituted imidazole, lysine or methyl-glucamine are endowed with remarkable antiinflammatory, antiaggregating and antithrombotic properties.

TABLE 1

R	Ex.No.	Melting point; I.R.
$CH_3-CH(CH_3)-CH_2-$	3	p.f.: 194-196.
	3a	p.f.: 143-145; I.R.: 3300, 1660, 1530, 1305.
	4	p.f.: 212-214.
	4a	p.f.: 155-156; I.R.: 3280, 1645, 1540, 1300.
$HOOC-CH_2-CH_2-$	5	p.f.: 204(**).
	5a	p.f.: 150; I.R. 3325, 1700, 1640, 1550, 1300.
	6	p.f.: 257-259(***).
	6a	p.f.: 145-150; I.R.: 3270, 1640, 1530, 1310.
	7	p.f.: 233-235.
	7a	p.f.: 178-181; I.R.: 3030, 1650, 1520, 1305.
	8	p.f.: 256-257.
	8a	p.f.: 163-165. I.R.: 3025, 1660, 1500, 1300.
$EtOOC-NH-CH_2-$	9	p.f.: 153-155.
	9a	p.f.: 102-103; I.R.: 3100, 1650, 1510, 1330.
$EtOOC-NH-(CH_2)_5-$	10	p.f.: 161-163.
	10a	p.f.: 110-112; I.R.: 3310, 1640, 1525, 1300.
$HOOC-CH_2-CH_2-CH(NH-COOEt)-$	11	p.f.: 218-220.
	11a	p.f.: 167-170; I.R.: 3300, 1650, 1520, 1295.
	12	p.f.: 181-182.
	12a	p.f.: 155-156; I.R.: 3320, 1640, 1510, 1305.

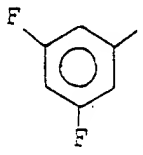
- continued -

TABLE 1 (follows)

R	Ex.No.	Melting point; I.R.
H-	13	p.f.: 236-238.
	13a	p.f.: 150-152; I.R.: 3310, 1630, 1530, 1300.
n-C17H35- (stearyl)	14	p.f.: 198-199 (*).
	14a	p.f.: 143-145; I.R.: 3300, 1650, 1560, 1310.
	15	p.f.: 235-240.
	15a	p.f.: 181-185; I.R.: 3310, 1650, 1580, 1315.
	16	p.f.: 185-186.
	16a	p.f.: 135-135; I.R.: 3310, 1640, 1525, 1300.
	17	p.f.: 230-232(****).
	17a	p.f.: 170; I.R.: 3100, 1640, 1570, 1305.
CH_3-	18	p.f.: 213-214(***).
	18a	p.f.: 151-152; I.R.: 3300, 1640, 1535, 1305.
linoleyl	19	p.f.: 159.
	19a	p.f.: 118-120; I.R.: 3320, 1650, 1530, 1300.
n-C19H39- (arachidyl)	20	p.f.: 160.
	20a	p.f.: 112-114; I.R.: 3320, 1650, 1525, 1300.
arachidonyl-	21	p.f.: 154.
	21a	p.f.: 127; I.R.: 3320, 1650, 1530, 1300.
	22	p.f.: 218-220.
	22a	p.f.: 115-119; I.R.: 3140, 1650, 1580, 1320.

- continued -

TABLE 1 (follows)

R	Ex.No.	Melting point; I.R.
	23	p.f.: 215-219.
	23a	p;f.: 97-98; I.R.: 3140, 1650, 1580, 1320.

(*) Known from E.P. 45,955;

(**) " " Biochem. Biophys. Res. Commun.-v.101, 258, 1981;

(***) " " Ger. Offen. 2,031,227;

(****)" " Biomed. Mass Spectrom, v. 11, 539, 1984.

EXAMPLES 24-28

According to the same methods of the previous claims, the following 5-acyloyl-amino-salicylic acids were prepared (I.R. values in cm^{-1} and elemental analysis in agreement):

24- 2-hydroxy-5-(4-cyclohexyl-butanoyl)-amino benzoic acid; m.p. : 196-198°C; I.R.: 3500, 3250, 1680, 1650, 1540, 1310;

25- 2-hydroxy-5-(2-(3-pyridyl)-acetyl)-amino benzoic acid; m.p. : 221-223°C; I.R.: 3510, 3260, 1680, 1640, 1540, 1300;

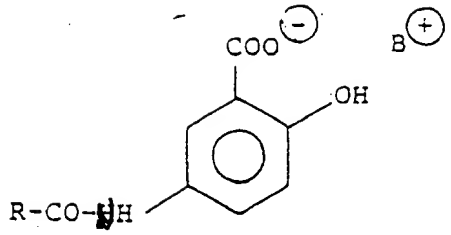
26- 2-hydroxy-5-(4-phenyl-benzoyl)-amino benzoic acid; m.p. : 178-180°C; I.R.: 3520, 3260, 1680, 1640, 1530, 1300;

27- 2-hydroxy-5-(m-trifluoromethyl-cinnamoyl)-amino benzoic acid; m.p. : 162-168°C; I.R.: 3500, 3250, 1660, 1635, 1500, 1300;

28- 2-hydroxy-5-(8-(1-imidazolyl)-octanoyl)-amino ben-

CLAIMS

1.



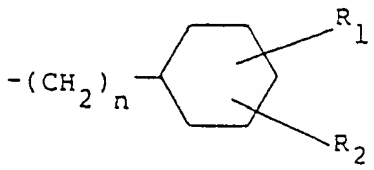
(I)

wherein:

$B^{(+)}$ is the imidazolium or C- or N-substituted imidazolium cation, lysine or similar basic aminoacids or methyl-glucamine;

R represents:

- hydrogen or a linear C_1-C_{25} alkyl chain, optionally substituted by one or more chlorine or fluorine atoms, free, etherified or esterified hydroxy groups, carboxy, carboxyalkyl, aminocarbonyl or N-substituted aminocarbonyl groups, one or more of the $-CH_2-$ groups being optionally substituted by keto groups;
- a chain of formula:



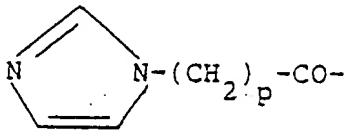
wherein n is an integer from 1 to 10 and R_1 and R_2, which may be the same or different, are H, halogens, $-OR_3$ or $COOR_3$ groups wherein R_3 is hydrogen or C_1-C_5 lower alkyl;

- a chain of formula:

$-(CH_2)_m-Het$

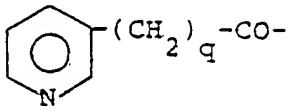
wherein m is an integer from 0 to 20 and Het is an optionally substituted 5- or 6-membered heterocyclic group containing one or more N, O or S atoms such as pyrrole, pyridine, furan, pyran, thiophene, oxazole, isoxazole, imidazole, pyrazole, thiazole groups;

- a chain of formula:



wherein p is an integer from 0 to 16;

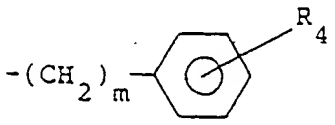
- a chain of formula:



wherein q is an integer from 1 to 16;

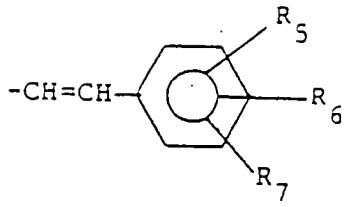
- an aryl or aralkyl residue such as phenyl; phenyl substituted by one or more fluorine or chlorine atoms, fluoroalkyl, alkoxy, alkoxycarbonyl, C_1-C_4 lower alkyl, amino dialkylamino, hydroxy, cyano groups or by groups of formula $NHCOR_3$ wherein R_3 has the above defined meanings; diphenyl; naphtyl groups;

- a chain of formula:



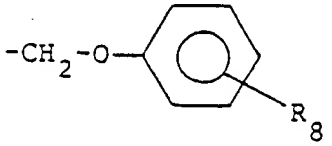
wherein m has the above defined meanings and R_4 is hydrogen or a linear or branched, saturated or unsaturated, C_1-C_{20} alkyl group;

- a chain of the formula:



wherein R_5, R_6 and R_7, which may be the same or different, are H, OR_3 (R_3 having the above defined meanings), NH_2, $NHCOR_3$, chlorine or fluorine atoms, fluoroalkyl groups;

- a chain of formula:



wherein R_8 is hydrogen, lower alkyl, fluorine or fluoroalkyl;

- a linear or branched chain of the formula:

$$-(CH_2)_n-X-\underset{\displaystyle R_3}{\underset{|}{CH}}-(CH_2)_{n'}-Y-$$

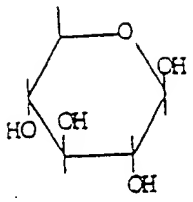
wherein R_3 and n have the above defined meanings, n' is an integer from 1 to 10 and X and Y are an oxygen, nitrogen, sulphur atom or a CH_2 group;

- a chain of formula:

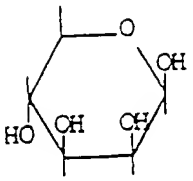
$$-(CH_2)_r-S-R_3$$

wherein r is an integer from 1 to 3 and R_3 has the above defined meanings;

- an aminoacid residue, namely L-leucyl, α or γ-L-glutamyl- in a free form or protected with the conventional amine protecting group, such as BOC;
- an Arg-Pro-D(Phe) chain or the like;
- an uronic residues of formula:



or



2. Compounds according to claim 1 wherein B is imidazolium or 2-aminoimidazolium.

3. A compound according to claim 1 wherein B is the imidazolium residue and the anionic component is selected in the group consisting of:

- 2-hydroxy-5-(2,4-dichlorobenzoyl)amino-benzoic acid;
- 2-hydroxy-5-hexadecanoyl-amino-benzoic acid;
- 2-hydroxy-5-isovaleroyl-amino-benzoic acid;
- 2-hydroxy-5-cyclohexylacetyl-amino-benzoic acid;
- 2-hydroxy-5-succinoyl-amino-benzoic acid;
- 2-hydroxy-5-benzoyl-amino-benzoic acid;
- 2-hydroxy-5-salicyloyl-amino-benzoic acid;
- 2-hydroxy-5-/4-(2',4'-difluorophenyl)salicyloyl-amino/-benzoic acid;
- 2-hydroxy-5-(N-ethoxycarbonyl)glycyl-amino-benzoic acid;
- 2-hydroxy-5-/(6-ethoxycarbonylamino)capropylamino/-benzoic acid;
- 2-hydroxy-5-(N-ethoxycarbonylglutamoylamino)-benzoic acid;
- 2-hydroxy-5-glucuronyl-amino-benzoic acid;
- 2-hydroxy-5-formyl-amino-benzoic acid;
- 2-hydroxy-5-stearoyl-amino-benzoic acid;
- 2-hydroxy-5-(4-methoxy)benzoyl-amino-benzoic acid;
- 2-hydroxy-5-(4-eptyloxy)benzoyl-amino-benzoic acid;
- 2-hydroxy-5-(4-fluoro)benzoyl-amino-benzoic acid;
- 2-hydroxy-5-acetyl-amino-benzoic acid;

- 2-hydroxy-5-linoleyl-amino-benzoic acid;
- 2-hydroxy-5-arachidyl-amino-benzoic acid;
- 2-hydroxy-5-arachidonyl-amino-benzoic acid;
- 2-hydroxy-5-(2,6-difluoro)benzoyl-amino-benzoic acid;
- 2-hydroxy-5-(3,5-difluoro)benzoyl-amino-benzoic acid;
- 2-hydroxy-5-(4-cyclohexyl-butanoyl)-amino-benzoic acid;
- 2-hydroxy-5-(2-(3-pyridyl)-acetyl)-amino-benzoic acid;
- 2-hydroxy-5-(4-phenyl-benzoyl)-amino-benzoic acid;
- 2-hydroxy-5-(m-trifluoromethyl-cinnamoyl)-amino-benzoic acid;
- 2-hydroxy-5-(8-(1-imidazolyl)-octanoyl)-amino-benzoic acid
- L-leucyl-5-amino-salicylic acid;
- γ-L-glutamyl-5-amino-salicylic acid;
- aceto acetyl-5-amino-salicylic acid.

4. As a novel compound, a compound selected in the group consisting of:

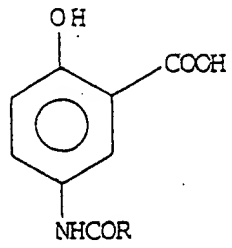
- 2-hydroxy-5-(4-cyclohexyl-butanoyl)-amino-benzoic acid;
- 2-hydroxy-5-(2-(3-pyridyl)-acetyl)-amino-benzoic acid;
- 2-hydroxy-5-(4-phenyl-benzoyl)-amino-benzoic acid;
- 2-hydroxy-5-(m-trifluoromethyl-cinnamoyl)-amino-benzoic acid;
- 2-hydroxy-5-(8-(1-imidazolyl)-octanoyl)-amino-benzoic acid.

5. A process for the preparation of compounds of formula I characterized in that the 2-hydroxy-5-amino-benzoic acid is reacted with acyl chlorides or anhydrides of acids having formula RCOOH, wherein R has the above defined meanings, and that the obtained N,O-diacyl derivatives are hydrolyzed in the presence of imidazole and subsequently

reacted with the base B.

6. Pharmaceutical compositions endowed with antiinflammatory, antiaggregant, antithrombotic activity containing as the active principle one or more of the compounds of claims 1-4.

7. Pharmaceutical compositions endowed with antiinflammatory, antiaggregant, antithrombotic activity containing as the active principle at least a compound of formula:



wherein R has the above defined meanings or of pharmaceutically acceptable salts thereof.

8. A method of treatment of inflammatory, thrombotic or hyperaggregating conditions in a living subject characterized by administering to said living subject a composition of claims 6-7.